HISTAMINASE IN THE TREATMENT OF URTICARIA AND ATOPIC DERMATITIS

A Preliminary Report

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Urticaria is frequently a perplexing problem, and with the exception of those patients whose disease disappears quite rapidly, the question of etiology and treatment is often difficult. In a like manner atopic dermatitis often causes great concern for both the patient and the doctor, and, as yet, a dependable therapy for many cases of either condition has not been discovered.

The purpose of this communication is to give the results of the use of *histaminase* in a small selected series of urticaria and atopic dermatitis. Unfortunately the amount of drug at our disposal was small, and so the report must be looked upon as preliminary. It is our hope to continue this work with a much larger group so that the results may be more convincing.

Many observers have suspected that the exudative reaction or spasm of smooth muscle characterizing various forms of hypersensitiveness are produced by the liberation of one or more chemical substances at the time of union of the antigen and antibody. Of all investigated substances histamine produces symptoms most resembling those of anaphylactic shock when injected into animals in toxic doses. As Tuft (1) stated, it seems more than mere coincidence that a simple chemical substance such as histamine can so closely imitate the symptoms of anaphylaxis.

Important experiments concerning histamine or a histamine-like substance (H-substance) in conditions of hypersensitiveness were carried out by Lewis (2), whose work dealt with the local vascular reactions of the skin to diverse stimuli. Lewis showed that regardless of the type of stimulus the skin reacted with a

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"triple response" consisting of: first an erythema due to local vasodilatation, second a diffuse flare caused by widespread relaxation of the neighboring arterioles and third a wheal produced by increased permeability of the vessel walls. The wheal was confined to the area of primary erythema. The identical typical response produced by merely stroking the skin of a person with dermographism could be reproduced by pricking a dilute solution of histamine into the skin. Therefore Lewis concluded that a diffusible substance either similar to or identical with histamine produced the local vasodilatation and wheal formation.

Subsequently Dale (3) showed that histamine was present in a large number of organs and tissues of the body, being apparently inert while in the cell but becoming active after being released by appropriate stimuli into the tissue fluids.

In 1925 Manwaring, Hosepian, Enright and Porter (4) showed by experiments on anaphylaxis in dogs that following contact with an antigen, injured cells, probably in the liver, liberated a histamine-like substance which caused contractions of certain smooth muscle structures (uterus, bladder and intestine). Their conclusions were based on the fact that blood taken from the liver of a dog in anaphylactic shock caused a similar syndrome when injected intravenously into a normal dog.

In 1932 Bartosch, Feldberg and Nagel (5), after extensive experiments on guinea pigs, found that after flooding the lung of a sensitized animal with antigen a substance could be isolated which had properties identical with those of histamine. The appearance of the substance depended upon the antigen-antibody reaction rather than upon other factors such as bronchial constriction, cessation of respiration or circulatory changes.

In the same year Dragstedt and Gebauer-Fuelnegg (6a) concluded from their experiments that in the majority of cases of severe or fatal anaphylactic shock in dogs a histamine-like substance could be recovered from the supradiaphragmatic vena cava and thoracic lymph duct. After further study (6b) the authors concluded that the substance was actually histamine.

Roth and Horton (7) in studying physical allergy found an increase in the gastric acids following immersion in cold water of the hand of a patient sensitive to cold. The increase strikingly paralleled that produced by the injection of 0.38 mgm. of histamine. The experiments of Roth and Horton suggested that the systemic reactions in patients hypersensitive to cold are caused by the absorption of histamine released in the cooled skin.

The possible importance of histamine in persons sensitive to cold is likewise indicated by the favorable response of such individuals to injections of histamine as reported by Bray (8).

Goodson (9), after surveying the subject of "physical allergy" formed the opinion that the urticarial wheals and some of the other manifestations of these forms of "allergy" might well be due to the presence of histamine in the tissues in greater amounts than can be dealt with by its physiologic antagonists.

Barsoum and Smirk (10) in 1936 measured increased amounts of H-substance in human blood taken from an arm undergoing reactive hyperemia to circulatory arrest. The authors believed that the liberation of the histamine-like substance during circulatory arrest accounted at least in part for the hyperemia. Code and Ing (11) have since shown that the histamine activity of the blood is actually due to histamine itself which can be extracted chemically from the white cells.

Such experiments also suggest that histamine already present in the tissues may be released by certain stimuli to give rise to abnormal reactions in the body.

Lewis (2) maintained that in urticaria there is an outpouring of H-substance into the tissues producing the characteristic wheals. The release of H-substance may be brought about either by external trauma or circulating noxae. Whether or not the substance is actually histamine is not definitely known.

Tuft (1) stated that of all the theories offered to explain the mechanism of allergic reactions in humans, that which involves the interaction between an allergen and reagin resulting in the formation or liberation of histamine or a histamine-like substance is the one most commonly accepted.

HISTAMINASE

Best (12) in 1929 noted the presence of a histamine inactivating substance in tissues when he demonstrated that ox or horse lung and other tissues (liver and kidney) caused the disappearance of naturally occurring or added histamine when the tissues were suspended in saline and incubated in the presence of toluene at 37°C. The experiments indicated that the histamine inactivating process might be an oxidative one. In 1930 Best and McHenry (13) investigated the question further emphasizing the fact that the transient effects following the intravenous or subcutaneous injection of small or moderate doses of histamine also suggest that the body may possess an efficient means of elimination or inactivation of the substance. It has also been shown that very little histamine can be recovered from the urine even after the intravenous injection of large doses. Best and McHenry found that the properties of the histamine inactivating substance are those characteristic of enzymes and suggested the name histaminase for the material which under experimental conditions produces a change in structure of the histamine molecule which is responsible for the loss of the physiologic activity of the amine. A study of the distribution of histaminase in the dog indicated that the kidneys and intestine are the richest source of the enzyme in this species. Their work indicated that histaminase produces a rupture of the iminazole ring in the histamine molecule since in test solutions the loss of iminazole content roughly parallelled the loss of histamine. They admitted however that little is really known about the mechanism of the histamine-histaminase reaction and that it might be either physical or chemical. They

also stated that since it had not been established definitely that histamine is the causative agent in any pathologic condition there was at that time no obvious clinical application even though it should be established that the ability of an organism to inactivate histamine can be increased by the administration of the enzyme.

Scholer's (14) work in 1933 suggested the presence of an anti-allergic principle in the intestine. In experiments with rabbits he produced local anaphylaxis (Arthus phenomenon) by the application of antigen to the stomach tissue, conjuctiva or skin of a sensitized animal while the similar application to the small intestine or appended mesentery produced no such reaction. He concluded that the intestinal mucosa possesses a distinct anti-allergic principle the chemical nature of which is unknown.

This protective or anti-allergic substance derived from the small intestine of the hog has been isolated and made available in a form suitable for peroral and parenteral administration. According to the manufacturers (15), histaminase or "Torantil" as it has been termed in Europe, is a protein-like material responding to chemical reactions common to albumins. It is a loose, white, stable powder, soluble in water, but showing a slight opalescent tinge after being dissolved. Histaminase is available in ampules, each dose representing 1 histamine detoxifying unit, and in tablets of 5 histamine detoxifying units. One unit represents the quantity of histaminase which is capable of detoxifying 1 milligram of histamine hydrochloride during 24 hours at a temperature of 37°C. The tablets are provided with a special coating which is insoluble in the gastric juice, so that the effect of the histaminase is exerted in the intestine.

In this preliminary report no attempt is made to completely review the literature concerning the clinical use of histaminase. Only a few pertinent articles will be cited with special reference to the use of the substance in dermatology.

Rigler (16) in 1936, stated that in his opinion histaminase has a desensitizing action on allergic conditions when administered parenterally or orally and that the product should aid greatly in solving the problem of allergy and intestinal intoxication.

W. Ercklentz and B. W. Ercklentz (17) in the same year wrote concerning the detoxifying and histamine-inactivating properties of histaminase. They felt that it was of great benefit in the treatment of gastritis, peptic ulcer, colitis, cirrhosis of the liver and asthma.

Moldenschardt (18), also in 1936, reported good results following the use of histaminase in gastric and duodenal ulcers, ulcerative colitis, and cirrhosis of the liver. Seborrheic eczema, pyoderma, and a case of primrose dermatitis also responded favorably. A case of angioneurotic edema was benefitted and in a case of serum sickness the writer gained the impression that the rapid subsidence of the eruption was brought about by injections of histaminase.

Urbach (19) also noted the successful treatment of a severe case of purpura in a woman aged 31 following the use of histaminase. The disease had not been influenced previously by the administration of vitamin C. Urbach concluded that in this instance the purpura was attributable to a deficient detoxifying function of the intestine. In discussing the patient Matras mentioned a case of chronic urticaria which had not been benefitted by injections of histaminase. Its oral use had not been tried.

Hartmann (20), in 1938, used histaminase in 25 severe cases of acne vulgaris, each of which had been fruitlessly treated for years by the commonly accepted therapeutic methods. The beneficial results were said to be astounding. The author stated that although the cause of acne is unknown there is basis for the belief that endocrine imbalance and metabolic disturbances play an important part. The histaminase was thought to have aided in the detoxification of substances in the digestive tract, which if absorbed, might produce a change in the skin, lowering its resistance to bacteria and hence leading to acne.

In 1937 Roth and Horton (6) reported distinct improvement following the administration of histaminase in a case of hypersensitiveness to cold. The patient before treatment developed swelling of the hand following its immersion in water at 10°C. for 7 minutes. Within a period of $4\frac{1}{2}$ days 67 units of histaminase

were given following which only 2 finger tips became swollen after the cold test in contrast to swelling up to the line of immersion previous to treatment. Histaminase also caused disappearance of abdominal distress of which the patient had complained following exposure to cold.

At a recent meeting of the Central Society for Clinical Research Foshay (21) reported on the effective treatment and probable prophylaxis of serum sickness by means of histaminase. Twenty patients were selected at random, most of whom presented a severe form of the disorder. Thirteen of 16 patients who were treated in the first or second day of the illness obtained relief in from 18 to 36 hours or less and in most cases the clinical responses were actually dramatic. Attempts at prophylaxis seemed extremely hopeful. Foshay commented that the treatment seemed rational, highly effective, safe and devoid of untoward by effects or after effects.

In discussing this work, Prickman stated that his results in the use of histaminase in vasomotor rhinitis were not outstanding (34 per cent relief). Roth reported that she was continuing to obtain good results in the treatment of hypersensitiveness to cold as well in hypersensitiveness to insulin. Foshay mentioned in closing the discussion that he knew of one patient with angioneurotic edema whose swelling was greatly reduced while he was taking histaminase but who again developed edema 9 to 14 hours after the cessation of injections or oral administration.

OUR OWN EXPERIENCE WITH HISTAMINASE

We began using histaminase in the treatment of urticaria in 1937 and have continued to administer it in selected cases since them. This study was limited to cases of several weeks' duration of which the cause could not be determined and which had proved refractory to the usual therapeutic measures such as calcium, ephedrine, adrenalin, autohemotherapy, strontium bromide etc. An attempt was made to exclude cases of which the causes were obvious and those of short duration which might well have involuted spontaneously or under the influence of various other forms of treatment. The patients receiving histaminase were given no other treatment. Papular urticaria was entirely ex-

cluded from the study. In most instances histaminase was given both by intramuscular injections 1 to 3 times weekly as well as by mouth, 2 or 3 tablets three times daily. No unfavorable reactions to the drug were noted.

On several occasions the investigation was interrupted on account of the difficulty of obtaining a sufficient supply of the medication; and for this reason the number of cases which were

TABLE 1

Urticaria—17 cases

RESULT	NUMBER OF CASES	REMARKS
Clinically cured	10 (59%)	In the cured cases the duration of treatment varied from 4 days to 3 weeks. Average time for cure 10.7 days
Improved	2 (12%)	One patient had urticaria for 9 months and was 50 per cent improved in 3 weeks. The second patient had urticaria for several years and was 90 per cent improved after 2 months treatment
Unimproved	5 (29%)	In the unimproved cases the durations were: 1, several weeks; 2, several weeks; 3, five months; 4, two years; 5, three and a half years

TABLE 2

Urticaria factitia—2 cases

No benefit in either case. One treated 3 weeks, the other 6 weeks.

TABLE 3

Atopic dermatitis—8 cases

No definite improvement in any. One month's trial of histaminase given, either without local therapy or without change in local therapy in use at the time of institution of histaminase.

studied is small. When an adequate supply of histaminase is again available we plan to continue the investigation in order that more definite conclusions can be drawn. For brevity the results are given in the tables 1 to 3.

COMMENT

On account of the small number of cases treated with histaminase no definite conclusions can be drawn concerning its value in

the treatment of urticaria. Our impression at this time however is that histaminase has some value in the treatment of the disease. It should be recalled that our 17 cases were of relatively long duration and had in most instances proved refractory to the usual therapeutic measures. In selecting our cases we kept in mind the fact that ordinary acute urticaria is a capricious disease and frequently undergoes spontaneous involution thus rendering difficult the appraisal of any particular type of treatment. These cases were not given histaminase until other measures had failed.

As is usually the case in other types of therapy, histaminase proved of no value in the 2 dermographic patients whom we treated.

One month's trial of the drug was given in the 8 cases of atopic dermatitis and in none was there enough improvement to warrant giving any credit to histaminase. In atopic dermatitis we believe that some degree of benefit should have been noticed within a month had the drug possessed much value in this disease. None of the patients were given dietary restrictions, sedatives or roentgenotherapy while taking histaminase. In most cases no local therapy was given; in a few others who had been using a certain external application for some time the histaminase was merely added.

From our small series we feel that it is permissible to state that histaminase is a useful adjunct to other therapeutic measures in urticaria and that further studies in which the cases are not limited to chronic resistant ones, may prove that the drug is of considerable value.

We do not feel justified to conclude that the favorable results are due to inactivation of histamine, yet we cannot deny the possibility. We must simply face the facts and admit that the nature of whatever anti-allergic properties histaminase possesses are as yet not definitely known.

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DISCUSSION

Dr. Paul A. O'Leary, *Rochester, Minn.:* I have been interested in the use of histamine in the urticaria group, in those with atopic dermatitis, and more recently in patients with light sensitivity. My former associate Dr. Williams started working with histamine with the idea of determining its physiologic effect in the atopic group. The results of these experiments were reported in the Journal of Investigative Dermatology. Skin temperature studies under accurately controlled conditions were made following the intracutaneous injections of histamine in patients with atopic dermatitis and normal individuals. In the atopic group, following the intracutaneous injection of histamine there was an increase in skin temperature in the face, the upper part of the neck, and the flexural surfaces of knees and elbows. The temperature at these points would rise as high as 3.5°C. in the atopic group while in the normal controls there was no appreciable temperature change in these areas. Accordingly, it seemed that histamine phosphate had a neuro-vascular action that increased the blood supply in the areas of predilection in patients with neurodermatitis. The therapeutic application of histamine on this basis produced variable results.

In the patients with light sensitivity results have been more encouraging following the use of histamine than in any other dermatosis in which we have used it. The administration of histamine in 0.2 mgm. dosage given two times a day for ten days in the early part of summer has carried several of the patients with light sensitivity through the summer without urticarial reactions after short exposures to sunlight. Repeating the course in midsummer has kept them quite free of skin lesions.

Dr. J. Gardner Hopkins, *New York:* I wish Dr. Laymon would tell us a little more about histaminase and the evidence that this is an enzyme. I would also like to ask whether after treatment he observed prolonged freedom of symptoms. This is hard to understand if the substance is a simple enzyme.

S. Rothman, *Chicago:* Some years ago I had the opportunity to treat 5 patients with the German histaminase preparation "Torantil." In these cases of chronic urticaria of unknown origin no beneficial effect could be observed. The mechanism of favorable results reported several times is difficult to understand. The liberation of histamine as the immediate cause of urticaria eruptions is not proved definitely. But even if this mechanism is assumed the attack hardly can be suppressed by histaminase because it does not prevent the histamine formation.

Dr. Marion B. Sulzberger, *New York:* I think Dr. Laymon's presentation very stimulating and having had a similar experience I can sympathize with the difficulties of obtaining the material. Moreover, I agree with everything that Dr. Rothman has just said. I do not believe it possible at present to adhere to

the theory that *all* whealing is necessarily due to the liberation of a histamine-like substance in the skin at the site of the wheal. More evidence is daily piling up against this hypothetical generalization. Whealing is a very complex phenomenon and may be of different pathogenesis and mechanism in different instances.

For example, Dr. Harold Abramson showed that if one puts histamine into the skin by iontophoresis, using one of the poles to force the chemical into the skin to produce a wheal, and then reverses the current one gets histamine out again. If however, one takes a wheal produced by the injection or iontophoresis of allergen in sensitive tissue and then attempts to get histamine out by reverse iontophoresis one is uniformly unsuccessful. Many other items of evidence today caution against the assumption that a histamine-like substance is always liberated in the production of whealing and that H-substance is the only substance concerned in whealing.

A few years ago Dr. Rostenberg and I attempted some experiments with the Winthrop Company's histaminase (T 360). We injected histaminase into the skin and immediately afterwards injected small quantities of histamine. Whealing at this site was not reduced by the preceding injection of histaminase. We then used histaminase mixed with allergens. The whealing produced by the allergens in sensitive skins was not reduced by the fact that we had mixed histaminase in our solutions. Moreover, as a third experiment, we incubated histaminase with histamine in vitro and got no reduction in whealing as compared with controls. Thus our results were definitely negative, even as regards the effect of the ostensible histaminase upon histamine in vitro. We never published these studies because of difficulties similar to those which Dr. Laymon has described; and because the Winthrop Company then recognized that their product was unstable—and have now prepared and recently placed at our disposal histaminase in a more reliable and stable form. However, even in theory the beautiful concept of histaminase reducing and stopping whealing is not adequate to explain why, in treating urticarial reactions and urticaria, one should expect more than a transitory effect through the destruction of histamine. Since even in theory the method cannot *prevent* histamine formation, one would expect only a brief respite when histamine is destroyed, similar to the brief benefit achieved in urticaria with adrenalin.

I too have found histaminase of some value in certain cases due to photosensitivity. This suggested the possibility of using histaminase in lupus erythematosus and other light-sensitive dermatoses, and we are now proceeding in this direction.

Dr. Carl W. Laymon, *Minneapolis:* The various discussions were greatly appreciated. I did not mean to give the impression from this presentation that it was possible to conclude that urticarial wheals are the result of the liberation of histamine and yet we cannot be entirely sure that histamine does not play some part in the process.

The exact action of histaminase upon histamine is not known although Best and McHenry's work indicated that the inactivation of the amine might be due to splitting up of the iminazole ring.

Dr. Hopkins brought out the point that if the relief in urticaria following the administration of histaminase were due to inactivation of histamine the lesions

should recur upon cessation of the drug. This is a difficult question to answer. Urticaria is a capricious disease and it is well known that even without therapy the condition may undergo spontaneous remission or cure.

I was glad to hear of Dr. O'Leary's favorable results in cases of hypersensitivity to light. As yet we have not used histaminase in such instances.

As I mentioned in reporting our results, the study was repeatedly interrupted by inability to procure histaminase. I have been told however that in the near future ample amounts of the drug will be available and that the new product will be much superior to that which we have been using.